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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
GOLDBERG, JEANINE ANNE

ART UNIT	PAPER NUMBER
1634	

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23

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/462,635	SCHMIDT ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-22 and 42-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-22 and 42-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed June 21, 2002 and September 23, 2002. Currently, claims 14-22, 42-49 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

2. This action contains new grounds of rejection necessitated by amendment.

New Grounds of Rejection Necessitated by Amendment

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 14-22, 42-46, 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rothberg et al. (US Pat. 5,871,697, February 16, 1999) in view of Dynal Catalog (1995) and further in view of Van Ness et al. (US Pat. 5,667,976, September 1997).

Rothberg et al (herein referred to as Rothberg) teaches a method for categorizing nucleic acid by

(i) digesting double-stranded nucleic acid with an endonuclease to produce a nucleic acid population, wherein the endonuclease is selected such that each nucleic

acid in the resulting nucleic acid population has sticky ends of a known base sequence and of a known common length (col. 9, lines 42-43);

(ii) contacting the nucleic acid population with an adaptor to ligate the adaptor to a termini of each nucleic acid in the population such that the adaptor has a double stranded primer portion having a known base sequence and a single stranded portion complementary to the known sticky end of the nucleic acids of the population (col. 9, lines 43-56);

(iii) contacting the nucleic acid with one or more oligonucleotide sets (57-60) and

(iv) categorizing the nucleic acid by isolating nucleic acid which correctly hybridizes to an oligonucleotide set, wherein each oligonucleotide sequence in each oligonucleotide set has a pre-determined recognition sequence such that the recognition sequence is situated in the portion of the nucleic acid which was double stranded after digestion with the endonuclease (limitations of Claim 4, 7).

Simply, Rothberg teaches that following cDNA preparation, the next step is simultaneous RE cutting of and adapter ligation to the sample cDNA sequences (col. 48, lines 42-44). As seen in Figure 2D the oligonucleotide 222 comprises a segment complementary to the adaptor, the overhang/sticky end, the restriction endonuclease site and the double stranded nucleic acid (limitations of Claim 5, 8). Rothberg teaches that primers are preferably constructed with a subsequence 226 of P nucleotides. Length P is preferably from 1 to 6 and more preferably either 1 or 2 (col. 51, lines 49-56)(limitations of Claim 9, 10, 11). Rothberg teaches that if necessary, prior to the first step, the cDNA sample is prepared by methods commonly known in the art, such as

amplification (col. 47, lines 23-26 and col. 87, lines 15-31)(limitations of Claim 12). Rothberg teaches that the primer comprises at the 3' end of and contiguous with the longer strand sequence the portion of the restriction endonuclease recognition site remaining on the nuclei acid fragment terminus after digestion by the restriction endonuclease...contiguous to said one or more additional nucleotides, and optionally such that said primers comprising a particular said one or more additional nucleotides can be distinguishably detected from said primers comprising a different said one or more additional nucleotides (col. 11, lines 20-39). Rothberg teaches why a primer complementary to a portion of the double-stranded nucleic acid is preferable "the joint result of using primers 223 with subsequence 226 in multiple PCR reactions after one RE/ligase reaction is to extend the effective target subsequence from the RE recognition subsequence by concatenating onto the recognition sequence a subsequence which is complementary to subsequence 226 (limitations of Claim 37). Thereby, many additional target subsequences can be recognized while retaining the specificity and exactness characteristic of the RE embodiment (col. 52, lines 6-14). Rothberg explicitly teaches that restriction enzymes (RE's) such as those known as class IIS restriction enzymes, which produce overhangs of unknown sequence are less preferable (col. 41, lines 12-15). Rothberg teaches that preferred REs have a 6 pb recognition site and generate a 4 bp 5' overhang. The RE embodiments are also adaptable to a 2 bp 5' overhang, which is less preferred since 2 bp overhangs have a lower ligase substrate activity than 4 bp overhangs (col. 42, lines 5-9). Rothberg specifically teaches that adapter 250 is specific for the RE BamHI, as it has a 3' end

complementary to the 5' overhand generated by BamHI (col. 45, lines 64-65). Similarly, Adapter 251 is specific for HindIII.

Rothberg also teaches a kit which contains one or more restriction endonucleasese, adapters and primers of the instant invention (col. 25-26)(limitations of Claim 26-29, 32-36). Rothberg teaches that the primers are detestably labeled such that primer with differing said one or two additional nucleotides have different labels that can be distinguishably detected (col. 26, lines 30-32).

Rothberg does not specifically teach categorizing the nucleic acid by denaturing the nucleic acid population, immobilizing the nucleic acids via covalent linkage, extending the oligonucleotides, denaturing the double stranded nucleic acid, contacting the immobilized single stranded nucleic acid with a second set of oligonucleotides sequences, extending the oligonucleotide, denaturing and isolating the resulting non-immobilized nucleic acids.

However, Dynal teaches a method of generating and isolating non-immobilized single-stranded nucleic acid. Dynal teaches contacting a first set of oligonucleotide sequences, biotinylated primers, with the nucleic acid population. The single stranded primers hybridized, extended via PCR and then immobilized onto a Dynabead via the biotin (Figure 10.1) The double stranded nucleic acid is denatured and the non-biotinylated immobilized species is removed. The immobilized single-stranded nucleic acid is the contacted with a random priming or a specific labeled primer, a second set of oligonucleotide sequence, and extended to form a double-stranded nucleic acid. The

double stranded nucleic acid is the denatured and the resulting non-immobilized single stranded nucleic acid is isolated.

Moreover, Van Ness teaches that covalently immobilized capture nucleic acid sequences have certain improved properties over non-covalently attached capture nucleic acids. Van Ness teaches that covalently captured oligonucleotides can withstand denaturation temperatures in excess of 90 degrees C for 10 minutes. Additional advantages taught include improved capture rate, quantity of immobilized capture nucleic acid can be increased approximately 20-fold, and ease in manufacturing. Van Ness teaches that the advantages contribute to greater sensitivities (col. 2, lines 40-55).

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Rothberg with the teachings of Dynal and further in view of Van Ness. The ordinary artisan would have been motivated to have performed the categorizing method of Rothberg and subsequently performed the method of Dynal to synthesize single-stranded probes in order to generate probes of known sequences in which were identified by the categorization method of Rothberg. Rothberg explicitly teaches that following the RE/ligase step is amplification of the doubly cut cDNA fragments such that any amplification method that selects fragments to be amplified based on end sequences is adaptable (col. 50, lines 5-8). The amplification method of Dynal is based upon the end sequences, thus would be considered an equivalent means of amplifying the cDNA fragments. The ordinary artisan would have been motivated to have amplified and

generated nucleic acid from a sample for subsequent analysis in the categorization method. Further modification of the amplification method of Dynal would be advantageous as provided by Van Ness for the express benefits taught by Van Ness. Therefore, the ordinary artisan would have been motivated to have substituted the non-covalent immobilization of Dynal with the covalent immobilization of oligonucleotides for the expected benefit of greater sensitivity. Moreover, it would be obvious to place these added reagents into the kit of Rothberg for the ability to easily perform the assay.

With regard to Claim 18, such that the oligonucleotide is contacted with the solid support prior to the nucleic acid population, it is well known that the primer may be contacted with the solid phase prior to the nucleic acid.

With regard to Claims 19-22, the teachings of Rothberg that oligonucleotides which has predetermined sequences of one or two bases would teach the ordinary artisan to use all of the possible combinations for the expected property of testing all possible combinations.

4. Claims 47-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rothberg et al. (US Pat. 5,871,697, February 16, 1999 or Rothberg et al. (US Pat. 5,871,697, February 16, 1999) in view of Dynal Catalog (1995) and further in view of Van Ness et al. (US Pat. 5,667,976, September 1997) as applied to Claims 14-22, 42-46, 49 above, and further in view of Hartley et al (US Pat 5,106,727, April 1992).

Neither Rothberg, Dynal nor Van Ness specifically teaches the incorporation of analogues into the oligonucleotides.

However, Hartley et al. (herein referred to as Hartley) teaches incorporating non-standard bases into random primers to reduce de novo synthesis.

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Rothberg in view of Dynal and Van Ness to include the non-standard bases as taught by Hartley for reducing the de novo synthesis. The ordinary artisan would have been motivated to have reduced the amount of de novo synthesis to obtain results representative of the categorized population as opposed to additional nucleic acid molecules.

Conclusion

5. No claims allowable over the art.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Thursday from 7:00AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Goldberg
November 21, 2002

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600